DETAILED ACTION

Claims 2, 12-13 and 17-21 are presented for examination.

Applicant's Amendment filed July 8, 2011 has been received and entered into the present application.

Claims 2, 12-13 and 17-21 remain pending and under examination. Claim 22 is cancelled. Claim 20 is amended.

Applicant's arguments, filed July 8, 2011, have been fully considered. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 12-13 and 17-20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Anagrelide Study Group ("Anagrelide, a Therapy for Thrombocythemic States: Experience in 577 Patients", *Am J Med*, 1992; 92(1):69-76; hereinafter "Anagrelide SG") in view of Hanson (U.S. Patent No. 6,585,995; 2003) and Mitchel et al. ("Transdermal Drug Delivery-Clinical and Regulatory Strategies", *American Academy of Dermatology Annual Meeting*, March 2000; Abstract) and further in view of Barnhart et al. (U.S. Patent No. 5,762,952; 1998), each already of record, for the reasons of record set forth at p.4-10 of the previous Office Action dated April 27, 2011, of which said reasons are herein incorporated by reference.

Claims 2, 12-13, 17 and 21 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Anagrelide Study Group ("Anagrelide, a Therapy for Thrombocythemic States: Experience in 577 Patients", *Am J Med*, 1992; 92(1):69-76; hereinafter "Anagrelide SG") in view of Hanson (U.S. Patent No. 6,585,995; 2003) and Mitchel et al. ("Transdermal Drug Delivery-Clinical and Regulatory Strategies", *American Academy of Dermatology Annual Meeting*, March 2000; Abstract) and further in view of Zupon et al. (EP 0252459; 1987), each already of record, for the reasons of record set forth at p.10-15 of the previous Office Action dated April 27, 2011, of which said reasons are herein incorporated by reference.

Response to Applicant's Arguments

Applicant traverses the instant rejections collectively. Applicant opines that, prior to the instant invention, it was unknown that the severity of cardiovascular side effects observed following oral administration of anagrelide to thrombocythemia patients was due to the 3-hydroxyanagrelide metabolite. Applicant asserts that the artisan, not knowing the cause of the side effects, would not have known whether the cardiovascular side effects in thrombocythemia patients could be reduced or how to do so. Applicant states that it was surprisingly discovered that transdermal administration of anagrelide minimizes these adverse effects that occur with oral administration of anagrelide because the plasma concentration of 3-hydroxyanagrelide is reduced. Applicant cites to Dr. Franklin's Declaration in support, stating that the fact that the 3-hydroxyanagrelide metabolite causes undesirable side effects represents the opposite of the expected metabolic detoxification process that occurs in the liver. Applicant argues against Hanson, stating that Hanson's listing of oral and transdermal administration is evidence that he did not appreciate the differences between the two modes of administration, and further alleges that Hansen teaches that thrombocythemic patients are not intended to be within the scope of his invention. Applicant

argues against the application of Mitchel, Barnhart and Zupon, stating that the references do not teach the claimed invention.

Applicant's traversal has been fully and carefully considered, but fails to be persuasive.

Firstly, Applicant opines that, prior to the instant invention, it was unknown that the severity of cardiovascular side effects observed following oral administration of anagrelide to thrombocythemia patients was due to the 3-hydroxyanagrelide metabolite and that the artisan, not knowing the cause of the side effects, would not have known whether the cardiovascular side effects in thrombocythemia patients could be reduced or how to do so. This is unpersuasive. One of skill in the art at the time of the invention would not have needed to pinpoint the precise identity of the metabolite responsible for these cardiovascular side effects associated with oral administration of anagrelide in order to seek alternative routes of administration that minimized side effects associated with metabolism of the active agent anagrelide. In fact, the knowledge in the prior art that oral administration of anagrelide to thrombocythemic patients was associated with cardiovascular side effects would have been clear motivation for one of ordinary skill in the art at the time of the invention to employ other routes of administration. This fact, coupled with the fact that Mitchel et al. teaches that transdermal administration was well known in the art to avoid first pass metabolism of a drug that can result in toxic or non-toxic metabolites thereof, and, therefore, would have been a route of administration that the skilled artisan would have availed himself of in order to minimize the side effects of first-pass liver metabolism, provides clear evidence of obviousness. It is immaterial that the art was not *per se* aware of the identity of the particular metabolite sought to be minimized because the art was clearly aware that transdermal administration avoids first pass liver metabolism generally and, therefore, would have reduced the metabolism of anagrelide into any toxic metabolite, including 3-hydroxyanagrelide, with the added benefit of delivering a more even level of drug over time, as evidenced by Mitchel et al.

In making such a combination of elements (i.e., transdermal administration of anagrelide for the treatment of a patient with thrombocythemia), the skilled artisan would have necessarily considered the prior art generally available at the time of the invention regarding the claimed elements, uses of the claimed elements and reasons or suggestions to combine such elements. The fact that Applicant has identified the source of the side effects as the reason to avoid oral anagrelide administration cannot be the basis for patentability when this same therapeutic advantage would have necessarily occurred within the usual practice of this combination and would have been a result that would have flowed naturally from following the suggestion of the prior art. Even though the prior art does not particularly disclose that transdermal administration of anagrelide minimizes the plasma concentration of the particular metabolite 3-hydroxyanagrelide, this is peripheral to the fact that the art clearly provides a reason to employ transdermal administration of anagrelide in order to avoid first pass liver metabolism of anagrelide and the unwanted side effects as a result of the metabolism. Thus, employing transdermal administration would have naturally commended itself to one of ordinary skill in the art at the time of the invention and would have necessarily resulted in the claimed effect in reducing the plasma concentration of the offending metabolite to which the cardiovascular side effects are attributed, absent evidence to the contrary.

Secondly, Applicant asserts that transdermal administration of anagrelide surprisingly minimizes these adverse effects that occur when anagrelide is administered orally because the plasma concentration of 3-hydroxyanagrelide is reduced. This is unpersuasive. Though Applicant has identified the particular metabolite responsible for the adverse cardiovascular side effects resulting from oral anagrelide administration, this cannot be considered unexpected because the art was already aware that transdermal administration of an active drug avoids first pass liver metabolism that would break down the drug into this metabolite. Thus, Applicant has merely demonstrated, both in the submitted remarks and in the previously submitted Declaration of Richard Franklin, what would have been expected to be observed if

the anagrelide was administered transdermally as opposed to orally, i.e., namely that the plasma concentration of anagrelide metabolites is reduced. This knowledge that transdermal administration avoids this same liver metabolism that ensues following oral administration is clearly documented in the cited prior art to Mitchel et al. The fact that Applicant has identified the metabolite to be avoided is not, in and of itself, an unexpected or surprising result because the art was already aware that metabolites resulting from first pass liver metabolism could be minimized via the use of transdermal administration. What is expected cannot be considered unexpected if the artisan was already aware that the effect under dispute would have occurred. The presence of an expected property is evidence of obviousness, just as the presence of an unexpected property or the absence of an expected property may be evidence of non-obviousness. MPEP §716.02(a).

Thirdly, Applicant cites to Dr. Franklin's Declaration in support, stating that the fact that the 3-hydroxyanagrelide metabolite causes undesirable side effects represents the opposite of the expected metabolic detoxification process that occurs in the liver. The submitted Declaration asserts that it would not have been expected that transdermal administration of anagrelide to minimize first-pass liver metabolism would have circumvented the adverse effects observed with oral administration of anagrelide. This position in untenable, however, because the artisan would have expected that transdermal administration would avoid first pass liver metabolism that occurs with oral administration and, thus, would have avoided these adverse effects associated with metabolism. Contrary to the Declarant's urgings, this effect or property of transdermal administration is well documented in the art (see, e.g., Mitchel et al.) and, therefore, cannot be an unexpectedly surprising effect. Moreover, though the Declarant cites to Examples in the as-filed specification in support of this allegedly surprising effect, the Examples appear to demonstrate nothing more than what would have been expected by the artisan, i.e., less metabolite was present in the plasma when anagrelide was administered transdermally as opposed to anagrelide administered orally. In addition, the Declarant urges that the 3-hydroxyanagrelide metabolite

causes undesirable side effects represents the opposite of the expected metabolic detoxification process that occurs in the liver. However, this is based upon an unsupported assumption that liver metabolism of a drug only results in detoxication. First pass liver metabolism can result either in toxication or detoxication of a chemical agent and, thus, the fact that the 3-hydroxyanagrelide metabolite causes side effects does not, *per se*, contradict the expected metabolic detoxification that would have occurred in the liver because liver metabolism can result in toxication or detoxication of the drug.

Fourthly, Applicant argues against Hanson, stating that Hanson's listing of oral and transdermal administration is evidence that he did not appreciate the differences between the two modes of administration, and further alleges that Hanson teaches that thrombocythemic patients are not intended to be within the scope of his invention. This is unpersuasive because, while it may be true Hanson does not particularly describe the differences between oral and transdermal administration of an active drug, the art at the time of the instant invention was well aware of such differences as evidenced at least by Mitchel et al. and, thus, such differences would have been understood to be inherently present in the recitation of each route of administration as an alternative means of administration.

In response to Applicant's allegation that Hanson expressly excludes the treatment of thrombocythemic patients from the scope of his invention, this is unpersuasive. Hanson expressly excludes the treatment of thrombocythemic patients from the scope of his *inventive* method because the art already recognized the therapeutic administration of anagrelide for the treatment of thrombocythemia patients. This is evident in the passage cited by Applicant, which appears at col.9, l.67-col.10, l.5, which states, "Subjects for whom the method of the invention are not intended are those diagnosed with conditions which already call for treatment with an agent such as anagrelide, i.e., secondary thrombocytosis, essential thrombocytosis, polycythemia vera, chronic myelogenous leukemia, and myelofibrosis." Thus, Hanson acknowledges that the art was already aware of the therapeutic benefit of using anagrelide for thrombocythemia and seeks to exclude this embodiment from his inventive method, .

This is because Hanson did not seek to remove from the public what was already in its possession. In view of the context of this disclosure, Applicant's attempt to demonstrate that Hanson teaches away from employing anagrelide in a transdermal form for the treatment of thrombocythemia is untenable and not found persuasive. The rejection stands.

Fifthly, and lastly, Applicant argues against the application of Mitchel, Barnhart and Zupon, stating that the references do not teach the claimed invention. This is unpersuasive. Applicant is reminded that rejections made under 35 U.S.C. 103(a) are based upon the combination of references. As a result, focusing solely on the discrete teachings of each of the cited references is tantamount to examining each of them inside of a vacuum and fails to be persuasive in establishing non-obviousness because it is the *combined* teachings that are the basis for a proper conclusion of obviousness, not each individual reference alone. In other words, it must be remembered that the references are relied upon in combination and are not meant to be considered separately. To properly conclude obviousness of an invention does not require the claimed invention to be expressly suggested in its entirety by any one single reference under 35 U.S.C. 103(a). Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. Please reference *In re Young*, 403 F.2d 754, 159 USPQ 725 (CCPA 1968) and *In re Keller*, 642 F.2d 413, 208 USPW 871 (CCPA 1981).

For these reasons *supra*, and those previously made of record at p.4-15 of the Office Action dated April 27, 2011, rejection of claims 2, 12-13 and 17-21 is proper.

Conclusion

Rejection of claims 2, 12-13 and 17-21 is proper.

No claims of the present application are allowed.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP §714.02 and §2163.06). Note

that support should be provided for amendments to previously pending claims, as well as any newly added claims. In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, not the published application. Due to the procedure outlined in MPEP §2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. §102 or 35 U.S.C. §103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims and share an inventor or assignee with the instant application. A copy of such copending claims is requested in response to this Office action in order to assist the examiner with double patenting analysis in the application.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds Draper whose telephone number is (571)272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571)-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds Draper/
Primary Examiner, Art Unit 1629

October 7, 2011